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# **Benign Essential Blepharospasm: What We Know and What We Don't**

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## **■ Introduction**

Benign essential blepharospasm (BEB) is a cranial dystonia that can have debilitating functional and social effects. While previously considered a disease of psychogenic origin, much has been learned about the disease in the past 4 decades within the field of neurology and ophthalmology and several treatment advances have been made.

Despite this progress, several questions remain regarding the neurophysiology and genetic basis of the disease, as well as the effectiveness of treatments. Many patients with BEB remain difficult to treat. The purpose of the present chapter is to summarize what has been learned and has what yet to be discovered in this transitioning field of research.

## **■ Clinical Presentation and Patient Evaluation**

BEB is a disorder characterized by sustained, involuntary spasms of the orbicularis oculi, corrugator, and procerus muscles resulting in partial or total eyelid closure. The prevalence of BEB ranges from 1.4 to 13.3 cases per 100,000 people with onset typically between the fifth and seventh decades of life.<sup>1</sup> Symptoms often range from mildly increased blink rate to forceful eyelid closure sometimes leading to functional blindness. Patients with BEB may also develop mid-facial or lower-facial spasms, often referred to as Meige syndrome.<sup>2</sup> Another associated finding in a subset of patients is apraxia of eyelid opening (AEO), which is a nonparalytic inability to open the eyelids in the absence of muscle spasm due to loss of co-inhibition between eyelid protractors and retractors. AEO associated with BEB is, therefore, not a true apraxia and should be distinguished from other paralytic causes.<sup>3</sup>

The majority of patients report symptoms of dry eyes, irritation, and photophobia at the time of presentation.<sup>2,4,5</sup> Patients may also have sensory tricks that help break spasms or reduce the frequency of spasms such as traction on the eyelids, talking, singing, humming, or looking downward.<sup>6</sup> Chronic blepharospasm may lead to functional eyelid disorders including dermatochalasis, blepharoptosis, entropion, ectropion, or brow ptosis.<sup>2,7</sup>

Several clinical rating scales are available to measure severity of BEB: the Jankovic Rating Scale, Blepharospasm Disability Scale, the Functional Disability Score, the Blepharospasm Disability Index, and a more recently validated blepharospasm severity scale developed by Defazio and colleagues.<sup>8–12</sup> Although the Jankovic Rating Scale has been used frequently in clinical trials, only the Blepharospasm Disability Index and the recent severity scale by Defazio and colleagues have undergone successful clinometric testing and validation.<sup>13,14</sup>

### **What We Don't Know**

The clinical manifestations of blepharospasm are characteristic, but limited evidence exists to explain the heterogeneity in disease severity between patients. It is unknown if AEO, which occurs in a minority of patients, represents a more severe spectrum of the disease, or a separate category of disease unto itself. Although ratings scales and electromyography (EMG) have been used to track the course of the disease and response to treatments, no singular objective measure has been able to consistently yield a quantifiable data point for researchers to study in this complex disease, which has many unique manifestations.

## **■ The Neurophysiology of Blepharospasm**

Overend first postulated the existence of a blink reflex motor pathway in humans in 1896,<sup>15</sup> and subsequent EMG studies have elucidated 2 components of the reflex in response to a facial tap.<sup>16</sup> The R1 component is recognized as an early response ipsilateral to the stimulus preceding the blink, and the R2 component is a late bilateral second response coinciding with the blink. This pathway is currently referred to as the trigeminal blink reflex. Other EMG studies have demonstrated abnormalities in both R1 amplitude and duration as well as R2 reflex duration and recovery in BEB. Inhibition of the R2 response is believed to be decreased in patients with BEB.<sup>17–19</sup>

Dopamine levels within basal ganglia (BG) pathways may be a key factor in BEB and other forms of dystonia. Early clinical observations in both rat studies and patients with dopamine-related disorders suggested a relationship between blepharospasm and dopamine insufficiency.<sup>20,21</sup>

Schicatanò and colleagues proposed a 2-factor rodent model for the pathophysiology of BEB. First, loss of dopamine in the substantia nigra may create a permissive environment in the trigeminal circuits. Second, weakening of the orbicularis oculi combined with dopamine loss led to characteristic findings of BEB in rats.<sup>22</sup>

Progressive loss of dopamine in the substantia nigra occurs with aging and is associated with increasing trigeminal reflex blink excitability, peaking in the fifth decade of life, which coincides also with the typical age of onset in BEB.<sup>23–26</sup> The presence of BEB in patients with Parkinson disease (PD) and tardive dyskinesia as well as patients with focal brain lesions involving areas such as the BG and thalamus also support a purported pathophysiologic role for dopamine in BEB.<sup>27–29</sup> Two recent interventional case series have demonstrated improvement in BEB symptoms with administration of oral methylphenidate, which increases intrasynaptic dopamine by blocking dopamine transmitters.<sup>30,31</sup>

Forty years ago, Marsden<sup>32</sup> argued that blepharospasm, like other focal dystonias, was linked to dysfunction of the BG. His argument was supported by subsequent work suggesting BG dysfunction as the underlying cause of BEB,<sup>18,22,33</sup> but the current leading theory argues that BEB is a result of defective neural circuitry rather than dysfunction at a single locus.<sup>18,34–36</sup>

### **What We Don't Know**

Despite significant advances in the understanding of the neurophysiology of blepharospasm, no unifying theory has emerged. Blepharospasm patients have heterogeneous clinical presentations, and the defective neural pathways underlying the disease may be heterogeneous as well. The emerging paradigm for blepharospasm and dystonia is the neural node hypothesis, which explains why many regions of the brain may be involved, and why patients may have different manifestations of the disease.<sup>29</sup>

## **■ Pathophysiology: Genetics of Blepharospasm**

BEB is generally considered to be a sporadic disorder, but up to 27% of patients have one or more family members with dystonia, suggesting some genetic predisposition.<sup>37,38</sup> Animal models and population studies have suggested that predisposing genes are inherited in an autosomal dominant fashion with low penetrance.<sup>39–41</sup> Studies have shown polymorphisms in the D5 dopamine receptor (DRD5), and a group of DYT polymorphisms have been linked to inherited dystonias, but results have been inconsistent.<sup>41–43</sup> Several other genetic mutations have been hypothesized as potential etiologies of BEB and other primary focal

dystonias, but no association between pure BEB and these mutations has been found.<sup>44–50</sup>

### ***What We Don't Know***

Despite identification of genetic loci associated with the disease, BEB does not have a strong genetic basis, and environmental stimuli clearly play a role in the manifestations of the disease. However, our understanding of the disease will evolve as we understand more about the interactions between known and as-yet-unknown genetic loci and the epigenetic phenomena occurring in response to the environment. At this point, we have limited information regarding clinical genetics that is useful for patient counseling.

## **■ Pathophysiology: Neuroimaging of Blepharospasm**

Advances in neuroimaging have suggested potential pathways for blepharospasm. Early studies using voxel-based morphometry to investigate gray matter abnormalities found increased gray matter volume in the putamen.<sup>51,52</sup> Subsequent studies have also found gray matter abnormalities in multiple areas of the cerebral cortex, but there are no common patterns based on voxel-based morphometry studies at this time.<sup>53–56</sup>

More recent functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have demonstrated abnormalities in the thalamus, pons, cerebellum, BG, and sensorimotor cortices. Together this data suggests that an abnormal cortico-striato-pallido-thalamic loop may be associated with the pathophysiology of BEB.<sup>57–67</sup> However, recent diffusion tensor imaging studies have been unable to clearly identify involvement of white matter tracts in BEB.<sup>56,68–70</sup>

### ***What We Don't Know***

Neuroimaging has made several advances since early studies of blepharospasm patients that suggested involvement of the BG in the pathogenesis of the disease. However, subsequent work has shown that the loci of the disease in the brain may be decentralized, with many areas of involvement including the BG and cerebellum. Neuroimaging may eventually provide insight into the etiology of BEB, but studies thus far have not identified a distinct pathway or locus to explain the manifestations of the disease.

## ■ Treatment of Blepharospasm

### ***Conservative Management Options***

Upon initial presentation, we provide all patients with information about the Benign Essential Blepharospasm Research Foundation (BEBRF). Anderson et al<sup>2</sup> found that 90% of patients had improvement in symptoms through the BEBRF. Ocular surface disease should be treated using artificial tears, eyelid hygiene, and temporary or permanent punctal occlusion.<sup>71</sup> Glasses tinted with FL-41 have been shown to improve subjective and objective symptoms.<sup>72</sup>

### ***Neurotoxin Injection***

Since the introduction of botulinum neurotoxin (BoNT) as a non-surgical treatment for BEB, it has become the treatment of choice for BEB. Use of BoNT in treating BEB involves addressing the overactive efferent motor limb of the blink reflex pathway. By causing flaccid paralysis of facial muscles via chemodenervation, symptoms of orbicularis oculi muscle spasms are reduced or eliminated temporarily. After local infiltration of BoNT into the synaptic space, the light-chain of BoNT is translocated into the presynaptic bouton where it cleaves the SNARE proteins required for exocytosis of ACh, resulting in a nonfunctional complex and attenuation of extracellular neurotransmitter release.<sup>73</sup> Diminished ACh release decreases the probability of firing an action potential required for muscle fiber contraction and results in localized flaccid paralysis.

The FDA approved BoNT for BEB and facial spasm in 1989 after a double-blind, placebo-controlled study demonstrated improvement in blepharospasm symptoms in 100% of patients compared with placebo.<sup>8</sup> Currently 3 brands of BoNT serotype A (BoNT-A) and one brand of serotype B (BoNT-B) have been approved by the FDA for the treatment of BEB and cervical dystonias. Studies have demonstrated similar efficacy between serotypes A and B and BoNT-B may be useful in patients who become refractory to BoNT-A.<sup>74</sup> However, BoNT-B may have a shorter duration of action and higher complication rates.<sup>75</sup>

Follow-up studies of BoNT have reported a response rate of around 90%.<sup>76-81</sup> However, many of the studies had small sample sizes and were based on patient-reported improvement. A 2005 Cochrane Review concluded that current studies suggested that BoNT was both highly effective and safe for BEB, but no high-quality randomized, controlled trials existed. Given the efficacy of BoNT, however, placebo-controlled trials may now be unethical to perform.<sup>82</sup>

Comparative studies of BoNT preparations have shown similar efficacy and safety between onabotulinum A toxin (BOTOX; Allergan Inc., Irvine, CA) and abobotulinum A toxin (Dysport; Ipsen Ltd., Paris, France).<sup>78,83-86</sup>

However, these studies used different dosing conversion ratios and a true equivalent dose ratio is still unknown. Two studies comparing BOTOX and incobotulinum A toxin (Xeomin, Merz Pharmaceuticals, Frankfurt, Germany) also showed similar efficacy and adverse effect rates using a 1:1 dosing ratio.<sup>87,88</sup>

On the basis of findings of recent published studies, the American Academy of Neurology has published practice guidelines for the use of BoNT for the treatment of blepharospasm, giving BOTOX and Xeomin Level B (probably effective) recommendations, Dysport Level C (possibly effective) recommendations, and concluded there was insufficient evidence to support the use of Myobloc in the treatment of BEB.<sup>89</sup> Benefits from BoNT may last as long as 15 years, but patients may require increasing doses over time to achieve the same benefit. Although rare, the most commonly reported adverse effects include periorbital hematoma, ptosis, dry eye, and blurry or double vision.<sup>90</sup>

### **Oral Pharmacologic Agents**

Historically, oral pharmacologic agents were first-line treatment for BEB before the era of BoNT. Older studies have suggested that trihexylphenidyl, baclofen, and benzodiazepines may be effective in treating BEB symptoms.<sup>2,6,91,92</sup> Others have recommended fluoxetine, clozapine, and the combination of valproate and baclofen to treat BEB symptoms.<sup>20,93,94</sup> Lithium has also been considered an effective treatment for BEB symptoms.<sup>95</sup> Although contradictory, treatments with both anticholinergic and cholinergic medications, as well as both dopamine agonists and antagonists, have been shown to help with BEB symptoms.<sup>91,95</sup>

Results from a more recent study showed that zolpidem may also be helpful in improving symptoms of blepharospasm and other dystonias by enhancing inhibitory pathways in the BG motor loop.<sup>96</sup> In 2 case series, oral methylphenidate has shown promise in treatment of BEB cases refractory to BoNT.<sup>30,31</sup>

At present, there is limited high-quality evidence to support the widespread use of oral pharmacologic therapies in BEB.<sup>97</sup> As BoNT has surpassed oral medications as the treatment of choice for BEB, oral pharmacologic treatments may be considered in cases refractory to BoNT and before pursuing surgical intervention.

### **Deep Brain Stimulation (DBS)**

In 2003, the FDA granted limited approval for DBS in treatment of certain types of dystonia. DBS has been studied mostly for movement disorders such as essential tremor or PD. Prior studies have included blepharospasm within the context of other dystonias, but few have studied DBS for pure BEB.

Multiple case reports have reported promising results for the use of DBS in treating medically refractory focal dystonias, including Meige syndrome.<sup>98–101</sup> Placement of unilateral DBS electrodes within the globus pallidus internus (GPi) showed bilateral benefit, although some cases required eventual bilateral lead placement. A recent report described successful bilateral GPi DBS surgery for a patient with isolated blepharospasm refractory to oral pharmacologic therapy, BoNT injection, myectomy and frontalis suspension surgery. DBS improved symptom severity and the patient had regained full independence after being functionally blind from the disease.<sup>102</sup>

Despite reports of DBS successfully treating medically refractory blepharospasm either alone or within other focal dystonias, there have also been studies stating that DBS may induce blepharospasm after stimulation of the subthalamic nucleus (STN), which is the preferred target in DBS for PD. It is known that blepharospasm is more common after STN DBS compared with GPi DBS.<sup>25,103–105</sup> STN DBS can reportedly induce tonic motor contraction of the facial muscles causing blepharospasm and AEO.<sup>103,106</sup> Complications of DBS surgery, although rare, may be severe and include hemorrhagic stroke and paralysis (1% risk per brain hemisphere), hematoma, infection, and hardware-related problems.<sup>107,108</sup>

## **Surgery**

Before the introduction of botulinum toxin injection for the treatment of blepharospasm, surgery was a common treatment modality. Differential sectioning of the facial nerve was first described in the early 1900s with good initial results.<sup>109</sup> Several others have described similar methods for facial nerve denervation including resection or injection of alcohol.<sup>110,111</sup> However, facial nerve surgery had a high rate of recurrence of symptoms from nerve regeneration as well as surgical complications related to the induced palsy.

Anderson and colleagues first described orbicularis myectomy in 1981 and it has become a mainstay of surgical treatment for BEB.<sup>7</sup> McCord et al<sup>112</sup> studied outcomes of facial nerve dissection compared with the Anderson myectomy technique and found patients who had undergone myectomy had lower rates of recurrence and required fewer additional procedures. Currently, myectomy is done in cases of BoNT injection failure, AEO associated with blepharospasm, and patients who are unable to receive BoNT injections.<sup>113</sup>

Traditionally, full myectomy involves removal of the pretarsal, preseptal, and orbital portions of both upper and lower eyelid orbicularis oculi muscle through blepharoplasty incisions as well as removal of the procerus and corrugator muscles.<sup>7</sup> More recently, upper eyelid myectomy alone has been shown to be effective in alleviating blepharospasm symptoms in the majority of patients, although some will require

eventual lower eyelid myectomy.<sup>114</sup> Upper and lower eyelid myectomy should be staged and performed at least 6 months apart to prevent lymphedema and scarring. Furthermore, the continued use of BoNT injection after upper eyelid myectomy may prevent or delay the need for lower eyelid myectomy and the effects of BoNT may last significantly longer after limited upper eyelid surgery.<sup>115,116</sup>

### **What We Don't Know**

The most significant advance in the treatment of blepharospasm has undoubtedly been BoNT therapy. Despite the efficacy of BoNT in many patients, however, there are still patients that remain symptomatic despite therapy, and require second-line treatments. Surgical myectomy has shown efficacy for patients with severe blepharospasm, but can induce cicatricial lagophthalmos. Postmyectomy patients may still require BoNT injections, albeit usually at a lower dose.<sup>116</sup> In both BoNT and surgical myectomy, the treatment has been directed at the motor neuron endplate and orbicularis muscle, and not at the underlying dysfunction of the blink reflex. Oral therapies have shown some promise for treating the underlying dysfunction in small case series, and deep brain stimulation has shown some isolated success. More work is needed in determining whether other oral agents, or emerging treatments such as transcranial magnetic stimulation, may help patients who do not respond to BoNT.<sup>117</sup>

### **■ Conclusions**

Many advances have been made in the understanding and treatment of benign essential blepharospasm since Marsden<sup>32</sup> classified the disease as a form of dystonia over 40 years ago. Despite these advances, many patients still remain difficult to treat and suffer significant functional disability from the disease. As much as we have learned about the disease, still more remains unanswered.

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